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CORRESPONDENCE

Acral lentigenous melanoma developing from the skin of bullous congenital ichthyosiform erythroderma

Dear Editor,

Various forms of carcinogenesis of melanoma have been proposed.[1] Among them, Wang and DuBois[1] reported that chronic inflammation could generate an immunosuppressive microenvironment favorable to tumor formation and progression.

In this report, we describe a case of acral lentigenous melanoma (ALM) developing in the lesional skin of bullous congenital ichthyosiform erythroderma (BCIE).

A 43-year-old Japanese woman visited our outpatient clinic with a 3-year history of a black plaque on her dorsal hand. She had been diagnosed with BCIE soon after birth. On her initial visit, physical examination revealed an asymmetric black macule on the dorsal side of her left hand (Figure 1A). Dermoscopy revealed an atypical reticular pattern, asymmetric globules and dots, irregular streaks and blue–white veil. According to dermoscopy findings, we treated this patient as having acral lentigenous melanoma (ALM) and excised the tumor with a 10-mm margin. Histological findings showed markedly atypical melanocytes arranged in irregular nests and solitary units at all levels of the epidermis to upper dermis (Figure 1B). Tumor thickness was 1.0 mm. From the above findings, we diagnosed this patient having ALM (pT1aN0M0 Stage IA). At the marginal area of the tumor, histological findings revealed hyperkeratosis, acanthosis, and granular degeneration in the epidermis (Figure 1C). Immunohistochemical staining revealed that these atypical melanocytes were positive for Melan A, HMB45, and programmed death ligand (PD-L)1 (Figure 2A), and surrounded by Foxp3$^+$ regulatory T (Treg) cells (Figure 2C). In addition, at the marginal area of the tumor, keratinocytes in the stratum spinosum expressed PD-L1 (Figure 2B) and Foxp3$^+$ Treg cells were scattered in the area adjacent to the basement membrane (Figure 2D). We screened for possible internal malignancy by positron emission tomography–computed tomography and found no evidence of metastasis.

BCIE is a dominantly inherited ichthyosis, frequently associated with mutations in keratin 1 or keratin 10 that result in disruption of the keratin filament cytoskeleton, leading to keratinocyte fragility.[2] Although BCIE patients typically display an abnormality in the permeability barrier function, and histological findings suggest chronic skin inflammation, little is known about the immunological background of BCIE.[2]

Since the expression of PD-L1 on cancer cells is reported to determine the prognosis in various types of cancer including

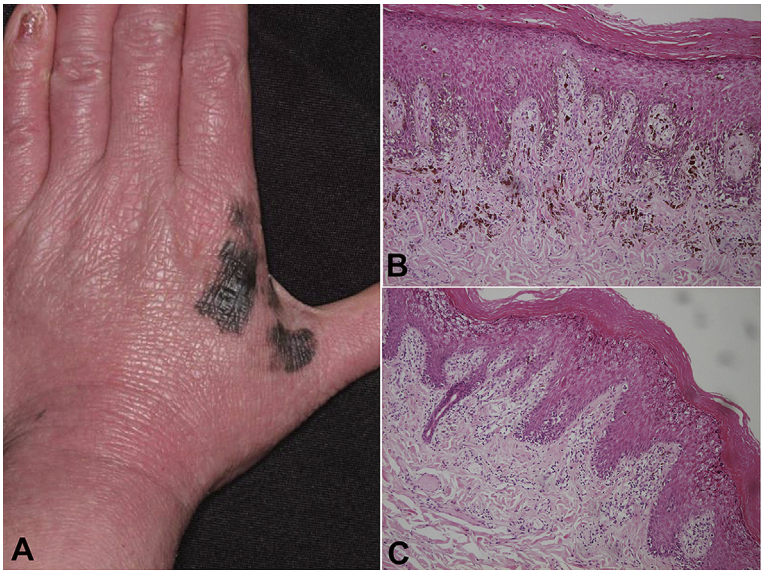

Figure 1 (A) Asymmetric black macule on the dorsal side of the left hand. (B) Tumor area: markedly atypical melanocytes arranged in irregular nests and solitary units in all levels of the epidermis to upper dermis. (C) Marginal area of the tumor: hyperkeratosis, acanthosis and granular degeneration in the epidermis.

Conflict of interest: The authors declare that they have no financial or non-financial conflicts of interest related to the subject matter or materials discussed in this article.

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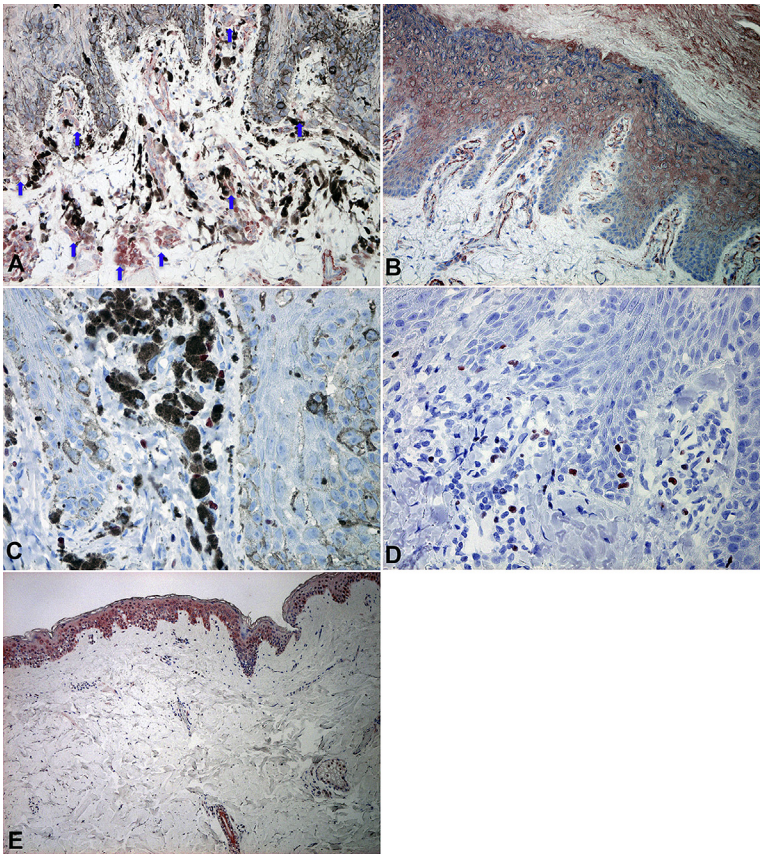

Figure 2 Paraffin-embedded tissue samples were deparaffinized and stained with (A,B,E) anti-PD-L1 antibody and (C,D) anti-Foxp3 antibody. (A–E) The sections were developed with liquid permanent red. (A,C: tumor area, B,D: marginal area of the tumor, E: normal skin) (Original magnification: A,B, 200×; C,D, 400×). At the tumor site, (A) atypical melanocytes expressed PD-L1, and were surrounded by (C) Foxp3$^+$ Treg cells. At the marginal area of the tumor, (B) keratinocytes in the stratum spinosum expressed PD-L1, and (D) Foxp3$^+$ Treg cells were scattered in the area adjacent to the basement membrane. (E) Normal keratinocytes expressed PD-L1. Foxp3 = forkhead boxP3; PD-L1 = programmed death ligand 1; Treg cell = T regulatory cell.

melanoma,[3] investigating the expression of PD-L1 is important for evaluating the malignancy. Concerning the normal skin, previous reports suggested that chronic skin inflammation induced PD-L1 on keratinocytes, leading the carcinogenesis of the skin.[3] Indeed, another report also suggested a correlation between chronic skin inflammation and carcinogenesis of the skin in inherited ichthyoses.[4] Concerning our present case, keratinocytes in the stratum spinosum strongly expressed PD-L1 in the marginal area of the tumor. Since PD-L1 promotes both the induction and maintenance of Treg cells,[5] chronic inflammation in BCIE might maintain the immunosuppressive microenvironment in concert with Treg cells.

Treg cells play a pivotal role in maintaining peripheral tolerance.[5,6] In the tumor site, Treg cells maintain the immunosuppressive microenvironment and promote tumor growth.[6] Notably, a recent report suggested that one of the possible anti-tumor effects of immunocheck point inhibitor, ipilimumab, is the depletion of Treg cells in the tumor site.[7] These reports suggested that Treg cells in the tumor site could be one of the prognostic factors for melanoma patients, and that depletion of Treg cells could be an optimal supportive therapy for human melanoma. Notably, compared to the normal skin, substantial numbers of Treg cells were detected in various skin inflammatory diseases such as psoriasis and atopic dermatitis.[8] These reports suggested that the long-term, continuous skin inflammation caused by BCIE might have promoted the development of melanoma in our case. Although this is the first English-language report of ALM accompanied by BCIE, we could not rule out the possibility of coincidence of ALM and BCIE. Therefore, to confirm our hypothesis, further cases and studies will be necessary.

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